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Failure to Demonstrate Any Hypoalgesic Effect of Low Intensity Laser Irradiation (830nm) of Erb's Point Upon Experimental Ischaemic Pain in Humans

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Background and Objective: **This study assessed the putative analgesic effect of low intensity, near-infrared laser irradiation (830nm; 1.5 & 9.0J/cm^2; continuous wave).**
Study Design/Materials and Methods: **The current study was completed under double-blind conditions using a standardised form of the submaximal effort tourniquet technique. Healthy naive female volunteers (n = 48) attended on two occasions for pain induction in the non-dominant upper limb, the first during which baseline data were obtained and on a second occasion during which subjects were randomly allocated to either control, placebo, or one of two treatment groups. In the treatment groups, irradiation was applied to ten points on the ipsilateral Erb's point immediately prior to the pain induction procedure at the parameters stated: For the placebo condition, sham "irradiation" was delivered by applying the laser unit without activating the probe. Pain was measured using computerised visual analogue scales and McGill Pain Questionnaires to assess "current pain intensity" and "worst pain experienced," respectively.**
Results: **Whereas analysis of variance and appropriate posthoc tests showed a trend toward hypoalgesia at a radiant exposure of 1.5J/cm^2, no significant effects of laser therapy were found.**
Conclusions: **These results do not provide convincing evidence for the clinical potential of low intensity laser irradiation as a pain relieving modality, at least at the parameters used. Further work is thus necessary to provide objective quantifiable data on the putative clinical efficacy of this modality and the relevance (if any) of irradiation parameters. Lasers Surg Med 20:69–76, 1997**

Key words: analgesia; experimental pain; laser therapy; biostimulation

INTRODUCTION

While the use of laser devices at relatively low intensities (<30J/cm^2) has recently captured the imagination of clinicians and the medico-scientific community as a potentially effective modality for the treatment of wounds and soft tissue injuries [1–3], the use of this therapy for the relief of pain has also attracted considerable scepticism from some sources [4–6]. The principal reasons for such scepticism are the generally poor quality of the research published within this field, the lack of any obvious mechanism of action, and the range of laser treatment parameters cited by au-

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thors. The continued preponderance of foreign language publications further confounds review of the literature on this application; consequently, the putative efficacy of laser therapy for the relief of pain remains debatable [2,4–7].

In spite of such controversy, results of several surveys of current clinical practice in laser therapy carried out at this centre have indicated the popularity and apparent efficacy of this modality for the treatment of pain of various aetiologies [8, 9]. As a consequence, in an effort to establish the positive impressions of survey respondents, we have previously completed several investigations of the hypoalgesic potential of this therapy upon experimental ischaemic pain under controlled laboratory conditions using the pulsed multisource/multiwavelength diode array cited as the most popular treatment unit in the surveys [7, 10–12]. In demonstrating a weak but significant treatment-mediated hypoalgesic effect with such therapy, the findings of these ischaemic pain studies corroborated the generally positive results reported in the literature from previous experimental work in animals [13–15] and in humans [16, 17].

Parallel studies at this centre have employed antidromic in vivo nerve conduction studies in humans to determine the effects of low intensity laser radiation upon peripheral neurophysiology and skin temperature. In contrast to the experimental pain studies already outlined, these neurophysiological investigations have relied upon the use of a single continuous wave 830nm infrared laser diode applied at relatively low radiant exposures ($\leqslant$9.0J/cm^2), rather than the higher dosage (31.9J/cm^2) multiwavelength irradiation used in the former at a variety of pulse repetition rates. These nerve conduction studies have consistently demonstrated laser-mediated effects that are critically dependent upon irradiation parameters [7, 18–21], and in particular, that the greatest increases in conduction latency (corresponding to decreases in conduction velocity) occur at a radiant exposure of 1.5J/cm^2 [20]. Although these results are interesting, their *precise* relevance to the putative hypoalgesic effects of these devices is unclear; thus the neurophysiological substrate(s) of laser-mediated pain relief remain occult. Nevertheless, if this neurophysiological effect does form any part of the substrates for the hypoalgesic effects claimed for these devices, one might expect good correlation between measured latency changes and hypoalgesic efficacy. Given the importance of establishing a scientific basis for the continued clinical application of this modality for the relief of pain, or indeed recommendation of cessation of its use in this application, investigation of the hypoalgesic effects of irradiation applied at the parameters used in the nerve conduction studies was considered to be indicated.

Thus the current investigation was undertaken to establish the analgesic efficacy of low intensity continuous wave laser irradiation using a single 830nm infrared laser diode probe upon the standardised variation of the submaximum effort tourniquet technique that had previously been used at this centre to investigate the effects of a multisource/multidiode array [7, 10–12]. To allow direct comparison with the earlier neurophysiological studies, laser was applied at two radiant exposures (1.5 and 9.0J/cm^2), representing the extremes of dosages used in these previous studies [e.g., 20].

MATERIALS AND METHODS

Recruitment Procedure

Ethical approval was obtained from the ethical committee of the University of Ulster for the current study for which female subjects, who had not previously participated in similar experiments and were unfamiliar with laser therapy, were recruited from staff and students of the university. For potential subjects, mutually convenient times were agreed for the two attendances necessary (see below). During first attendance, subjects received a comprehensive briefing on the relevant experimental procedures. All were expressly reminded of their right to terminate the proceedings at any point without necessarily giving a reason for doing so and their attention drawn to the limited dangers associated with the ischaemic pain induction technique. Each subject was then invited to ask any relevant questions and to sign a simple consent form. In keeping with the principles of informed consent, subjects were informed that low intensity laser therapy might be applied during their second attendance.

Screening Procedure

Subjects' nondominant arms, which were used in this experiment for the purposes of pain induction, were routinely examined prior to commencement of the ischaemic procedure at each attendance. It was further determined that subjects were currently healthy and free from any symptoms or illnesses that would contraindicate the

pain induction procedure. Subjects were specifically screened for peripheral neuropathy or vascular abnormality, hyper- or hypotension, as well as current drug usage or current menstruation. On the basis of this screening procedure, it was found necessary to exclude five subjects from the experiment; a total of 53 subjects were recruited, of whom 48 were eventually used in the experiment.

Pain Induction Procedure

Subjects were seated at a table in a controlled laboratory environment, with a microcomputer (520 ST, Atari, London, UK) used for the purposes of pain assessment mounted on the table directly in front of the subjects' chair. Once comfortably seated, subjects' nondominant arms were exposed to above the bulk of biceps/triceps and routinely examined as outlined above. When this was satisfactorily completed, operation of the computer's mouse control to rate pain (see below) was demonstrated.

An elastic bandage was then applied to the exposed hand and forearm under constant tension, up to a point ~ 8 cm above the elbow joint, and a sphygmomanometer cuff wrapped around the upper part of the limb over the bulk of biceps/triceps. With these in place, a dynamometer (Martin vigorometer) fitted with a medium-size balloon was used to assess maximal grip strength (MGS) in the arm. Thus assessed, a marker on the dynamometer was set to read 75% of this maximal value and subjects were asked to elevate the arm vertically above the head for a 60-second period in order to desanguinate the limb under the combined action of gravity and the elastic bandage. With the arm still vertical, the cuff was inflated rapidly (<2s) to a pressure of 250 mmHg. The point at which tourniquet inflation was completed was recorded as time zero, a timer started, and the first of 12 computerised Visual Analogue Scales (VAS) for subjects to rate current pain intensity (see below) at 1-minute intervals was presented. Once pain had been rated in this way, the arm was returned to a resting position on the table and, using the previously set dynamometer, subjects performed 20 hand grip exercises within the next minute, holding each grip for a period of 1 second. At the end of this second minute, a second VAS was presented for subjects to rate their current level of pain. It should be stressed that, although returning the arm to a resting position usually decreased the pressure in the tourniquet cuff, a constant pressure of at least 200 mmHg was maintained throughout the procedure.

Deflation

After the tenth VAS was presented, the tourniquet cuff was slowly deflated over a 2-minute period to allow subjects' forearms to resanguinate gradually. A further two VAS were presented during this period at 1-minute intervals as before. On conclusion of each experiment, the tourniquet cuff and elastic bandage were removed and subjects' forearms routinely examined to identify any obvious trauma, undesired side effects, or residual pain. No such problems were evident in the subjects used in this study.

Pain Measurement

Computerised VAS were used to assess current pain intensity at 1-minute intervals for the total duration of the procedure, including the deflation period (i.e., 12 minutes) as already outlined. At each minute point, a VAS was presented for a total of 15 seconds, with the marker on the VAS located halfway along the analogue scale for each new presentation of the scale, the position and orientation of which were randomised by the application program. Subjects used the integral click switch on the mouse to finalise and record the reading once they were happy that the position of the marker along the scale adequately reflected the current level of pain experienced. Each VAS reading was recorded by the program as a percentage of the total length of the analogue scale and automatically stored to disk for subsequent analysis.

In addition to this continuous rating of pain throughout the procedure, subjects were also interviewed using a single standard McGill Pain Questionnaire (MPQ) at the end of each attendance. The MPQ was selected to provide an additional measure of the quantitative and qualitative aspects of the *worst pain experienced* during the procedure; five pain scores were calculated from the completed MPQ: Sensory (S), Affective (A), Evaluative (E), Miscellaneous (M) scores, as well as an overall Pain Rating Index (PRI) score.

Second Attendance

After exactly 48 hours, subjects were required to attend a second pain induction session during which they were randomly assigned to one of four experimental groups: (1) control condition (neither active nor sham irradiation), (2) placebo condition, using the specified laser in contact with the subjects' skin but without activating the laser probe; (3) treatment condition 1, in which subjects

received a radiant exposure of 1.5J/cm^2 using an 830 nm GaAlAs continuous wave laser probe, and (4) treatment condition 2, in which subjects received a radiant exposure of 9.0J/cm^2 using the same laser.

For the purposes of this investigation, double-blind conditions applied with one investigator independently applying the treatment according to a predesigned master schedule and the second (who was ignorant of the other aspects of the experiment) inducing and recording pain to limit the potential for experimenter bias. Results were subsequently analysed independently.

Irradiation Parameters

Laser irradiation was administered immediately before pain induction commenced on the second attendance. Such irradiation was delivered using a GaAlAs 830 nm laser diode (CBM Master 3, CB Medico, Vaeloese, Denmark) applied perpendicularly in contact with the skin over the ipsilateral Erb's point. This point was identified at the junction of the midclavicle and the sternocleidomastoid muscle and was chosen to allow irradiation over the underlying brachial plexus, where the nerve trunks supplying the upper limb are most superficial. For the purposes of laser application, the skin overlying Erb's point was exposed, marked with a standardised array of 10 equally spaced points, and each point irradiated in quick succession for either 5 or 30 seconds per point to deliver the required dosages. The physical parameters of the laser unit used here were measured as: wavelength: 830 nm; average power output: 30 mW; area of spot size: 0.1 cm^2 irradiance: 300 mW/cm^2. Calibration of the laser was completed at the beginning of each experiment.

Using the equation:

$$\text{Time (s)} = \frac{\text{Radiant Exposure (J/cm}^2\text{)}}{\text{Irradiance (W/cm}^2\text{)}}$$

irradiation times to deliver radiant exposures of 1.5 and 9.0J/cm^2 were calculated to be 5 and 30 seconds per point, respectively, as already indicated.

Analysis

All data were analysed using analysis of variance (ANOVA) to determine whether observed changes between groups were statistically significant ($P<0.05$).

RESULTS

Visual Analogue Scale Scores

Results for subjects' first attendance are summarised in Figure 1, which plots VAS scores (%) for all groups against time (minutes); points show means ± s.e.m. for each group, which are labelled based upon subsequent (second attendance) group allocation. This graph clearly illustrates the progressive increase in pain intensity experienced by subjects during the first 10 minutes of this ischaemic pain induction procedure, followed by the rapid decrease in reported pain intensity during cuff deflation (Fig. 1).

Analysis of these data using repeated measures ANOVA showed no significant differences between groups, thus indicating subjects to be well matched for the procedure. To assess the effect of treatments compared to control, VAS scores were standardised for each subject by subtracting the values obtained during initial attendance from those obtained during second (i.e., final) attendance. Figure 2 plots such standardised VAS difference scores (mean ± s.e.m.) against time (minutes); with scores standardised in this way, hypoalgesia is represented by positive and hyperalgesia by negative values. Although no obvious trend was apparent from the results in the control group for the majority of the experimental procedure, a marked *hyper*algesic effect was observed in this group during the deflation period (i.e., at the 11th and 12th minute). In contrast, in the placebo group a mild hypoalgesic effect was evident up until the 6-minute point and again after the 10-minute point. However, during the most painful period of the procedure (i.e., 7–10 minutes), there was apparently a hyperalgesic or nocicebo effect of such sham irradiation. Of the two laser treatment groups, the 1.5J/cm^2 group showed some hypoalgesic effect after the 5-minute point, which became more marked by the 11th and 12th minutes of the procedure. However, results in the 9.0J/cm^2 laser treatment group were less clear cut. Although this group demonstrated some hypoalgesic effects until the 6th minute, the final minute of the procedure found a marked increase in pain in this group.

Standardised "difference" scores were compared between experimental groups using repeated measures and one factor ANOVA. Whereas the latter found some marginal differences between groups at the 12-minute point, repeated measures ANOVA failed to demonstrate differences between groups to be significant.

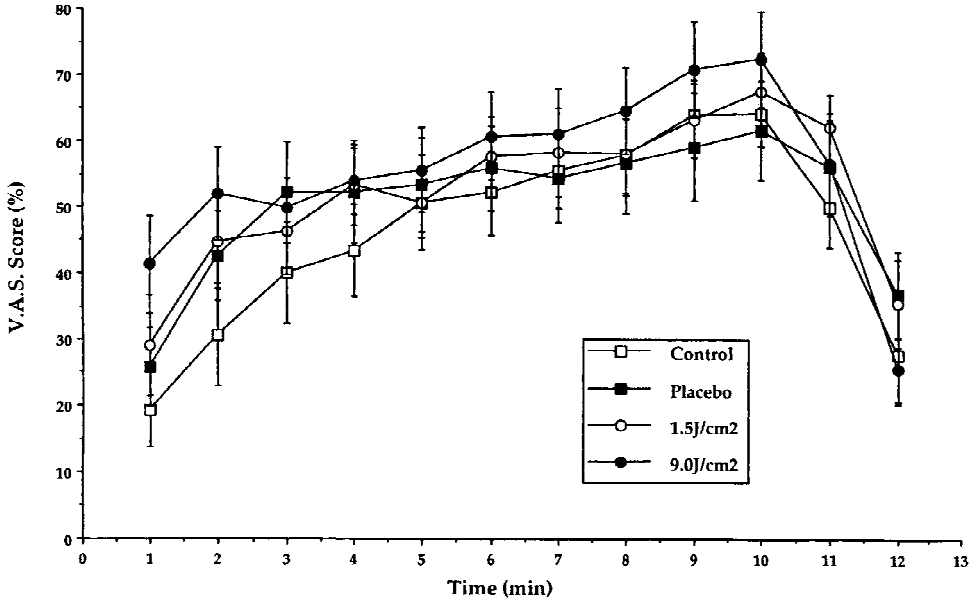

Fig. 1. Summary of Visual Analogue Scale (VAS) scores for initial attendance; (points show means ± s.e.m.).

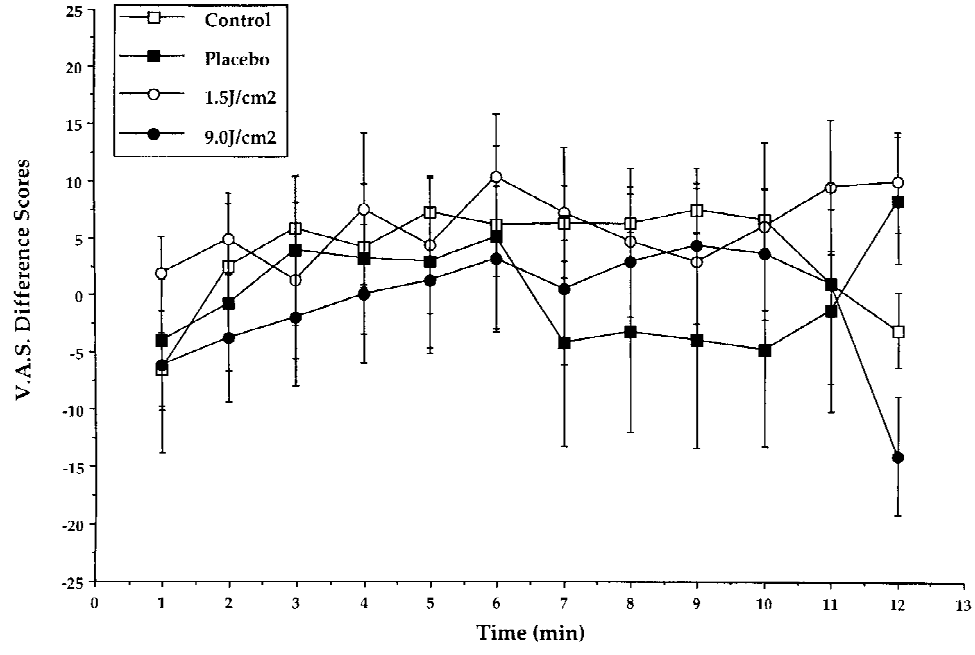

Fig. 2. Summary of differences in initial and final Visual Analogue Scale (VAS) scores; (points show means ± s.e.m.).

MPQ Scores

Figure 3 plots MPQ results, standardised as difference scores as for VAS, for the five components of the questionnaire; as for previous figures, points represent means ± s.e.m. for each group with hypoalgesia represented by positive and hyperalgesia by negative scores. This figure shows some consistent trends throughtout all components of the MPQ. Most notably, for the 1.5J/cm^2 laser group results demonstrated hypoalgesic effects in all but the Evaluative component of the MPQ. In contrast, results in the 9.0J/cm^2 laser group demonstrated an hyperalgesic effect with this level of irradiation, again in all but the Eval-

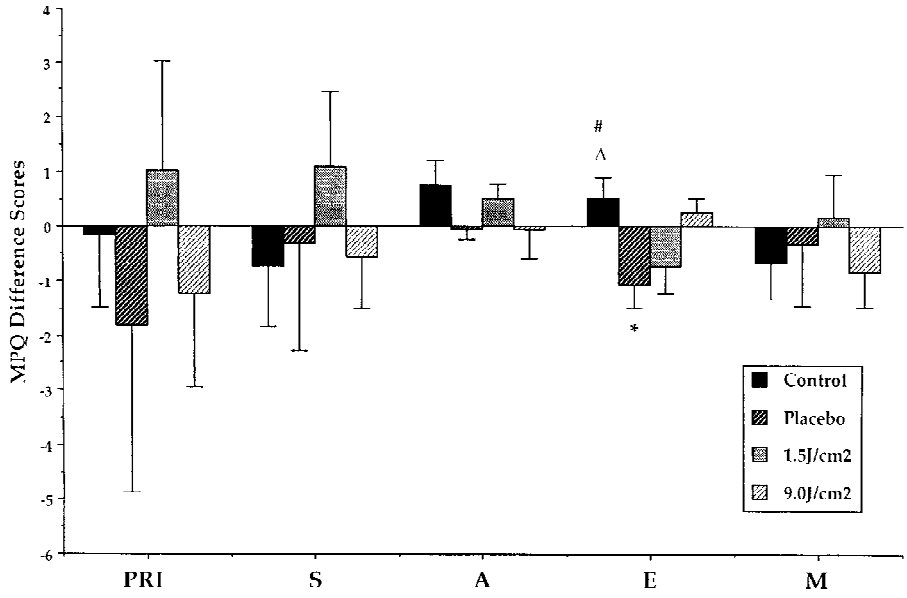

Fig. 3. Summary of differences in initial and final Pain Rating Index (PRI), Sensory (S), Affective (A), Evaluative (E), and Miscellaneous (M) scores from McGill Pain Questionnaires (MPQ); (columns show means ± s.e.m.). * represents significance between placebo and 9.0J/cm^2. △ represents significance between control and 1.5J/cm^2. # represents significance between control and placebo.

uative component of the MPQ. Perhaps most suprisingly, results for the placebo group also show a marked hyperalgesic (i.e., nocicebo) effect with sham irradiation. In the MPQ scores for the control group, no such consistent pattern was seen. MPQ data were analysed as standardised difference scores using one factor ANOVA, which showed statistically significant differences between experimental conditions for the Evaluative component of the MPQ ($P = 0.0213$); no such significant differences were seen for any of the other components of the MPQ. Corrected Fisher tests completed on the evaluative score data indicated there to be significant differences between the 1.5J/cm^2 laser treatment and control groups, the 9.0J/cm^2 laser treatment and placebo groups, as well as the control and placebo groups.

DISCUSSION

The putative hypoalgesic effects of low intensity laser irradiation remain controversial, mainly due to the poor quality of some of the publications within this field and the lack of an obvious mechanism of action [2, 4–7]. In the light of this, and on the basis of previous positive findings at this centre, the purpose of the current study was to investigate hypoalgesic effects of low intensity infrared laser irradiation applied at Erb's point upon experimental ischaemic pain in humans. As indicated ahbove, the standardised form of the SETT used here had already been successfully employed in the investigation of the hypoalgesic effects of combined phototherapy/low intensity laser therapy [7, 10–12] and thus seemed to represent a useful model of pain for the current study. In addition, nerve conduction studies at this centre have consistently demonstrated a laser-mediated effect upon conduction latency and that such observed effects are critically dependent upon irradiation parameters, and in particular radiant exposure, with 1.5J/cm^2 apparently representing the most effective dosage for slowing of conduction velocity [20]. If such peripheral neurophysiological effects upon nerve conduction latencies represent a substrate for the putative hypoalgesic effects of these devices, it might be expected that concomitant hypoalgesic effects would be seen at this dosage. Thus the current study used 1.5J/cm^2 as the radiant exposure for one of the laser treatment groups and a higher level of 9.0J/cm^2 for a second laser treatment group for comparison.

Analysis of the current results has provided little convincing evidence of the hypoalgesic effects of low intensity laser irradiation upon experimental ischemic pain at the parameters used here. However, data for the 1.5J/cm^2 laser group demonstrated some general trends toward hypoalgesia, most notably for the Evaluative aspects of the MPQ, in which results achieved significance.

An interesting (although nonsignificant) nocicebo effect was also observed with sham irradiation, most notably in the MPQ data. Although difficult to explain, this may be due to increased anxiety in these naive subjects who (perhaps) became apprehensive when the laser probe was applied, or due to the fact that a second experimenter was present to deliver the laser treatment.

In both laser groups it is interesting to note that even though neither group reached significance in the overall PRI scores from the MPQ, the 1.5J/cm^2 laser group showed a mild hypoalgesic effect, whereas 9.0J/cm^2 showed a *hyper*algesic effect (with the sole exception of E scores in both cases). This inverse relationship between effect and radiant exposure is in keeping with our previous findings at this centre, in isolated frog sciatic nerve preparations in vitro [21] and antidromic nerve conduction studies in the human median nerve in vivo [20]. Whereas in both these nerve conduction studies, the lowest radiant exposures used produced the greatest effects, the latter study in particular demonstrated that 1.5J/cm^2 produced the largest (and significant) laser-mediated increase in conduction latency, corresponding to a decrease in conduction velocity. However, given the current findings, this slowing of nerve conduction velocity probably does not represent a possible substrate of the mild hypoalgesic effects demonstrated here at the same radiant exposure.

Finally, although it might be suggested that ischaemic pan induction techniques may not represent the best method of assessment of the pain relieving effects of laser therapy, such techniques have been widely used and accepted as one of the best models of clinical pain for the laboratory assessment of putative pharmacological analgesics [22–26]. Furthermore, the standardised variant of the ischaemic technique described here also has been previously used to investigate the analgesic potential of other physical modalities, e.g., so-called H-wave therapy, a biphasic exponentially decaying electro-stimulation waveform, which has recently been promoted as an effective modality for the relief of pain [27], as well as conventional transcutaneous electrical nerve stimulation (TENS) [28]. However, the most convincing evidence for the suitability of the technique for the current study comes from our previous work on combined phototheraphy/low intensity laser therapy; in these studies, such *combined* treatment applied to Erb's point at relatively higher radiant exposures (>30J/cm^2) has consistently demonstrated a weak but significant hypoalgesic effect [7, 10–12].

Results of the current investigation thus serve to underline the necessity of additional laboratory-based work to establish definitively or otherwise the analgesic potential of this modality as a necessary precursor to any possible future *clinical* trials. However, the current results can in no way be seen as a definitive base upon which to initiate clinical studies. In addition, although not essential to determination of the efficacy of this modality, the putative mechanism of analgesic action of low intensity laser irradiation remains unclear and thus contributes to the scepticism surrounding this area. Thus the precise neurophysiological and hypoalgesic effects of this modality will only become apparent with further controlled studies.

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